

Developing an international network for breast cancer research: the BIG experience

Clin. Invest. (2011) 1(5), 623–628

With a network of 47 academic research groups worldwide, the nonprofit Breast International Group (BIG) is a leading force in the breast cancer research arena. BIG's mission is to facilitate breast cancer research internationally by stimulating cooperation between its members and other academic networks, such as the North American Breast Cancer Group. Global collaboration between groups with a shared vision is necessary to fight breast cancer efficiently. BIG members follow the same principles of research conduct, including strict rules about scientific integrity in trial design, trial governance, data management, independent data review and the reporting of results. This ensures that research advances knowledge to improve treatments and patient outcomes, while preserving independence from the pharmaceutical and biotechnology industry, even when BIG trials are supported wholly or in part by industry. Such balanced partnerships best serve the needs of patients. This article describes the development of BIG, highlighting its key achievements and plans for the future.

Keywords: academic research • breast cancer • international collaboration • lapatinib • letrozole • translational research • trastuzumab

The nonprofit Breast International Group (BIG) is a leading force in the breast cancer research arena and consists of a network of 47 academic research groups based in Europe, Canada, Latin America, Asia and Australasia. BIG's mission is to facilitate breast cancer research at the international level by stimulating cooperation between its members and other academic networks, and collaborating with, but working independently from, the pharmaceutical industry.

BIG also works closely with the US NCI and the North American Breast Cancer Group (NABCG) to identify difficult aspects of breast cancer research, focus on research areas not supported by the pharmaceutical industry and collaborate to resolve common problems. Such large-scale cooperation is crucial to make significant advances in breast cancer research, reduce the wasteful duplication of effort and optimally serve patients affected by the disease.

BIG's creation: vision & challenges

In the early 1990s, breast cancer research in Europe was highly fragmented, with academic groups running many similar trials, but not yet interacting in a way to facilitate collaboration. Martine Piccart and Aron Goldhirsch, respectively involved in the activities of the Breast Cancer Group of the European Organisation for the Research and Treatment of Cancer (EORTC) and the International Breast Cancer Study Group (IBCSG), together shared a different vision for the future: groups debating the implications of latest research findings, sharing ideas for new clinical trials and working in harmony to conduct those trials together, whether as solely academic studies or in partnership with industry. The realization of this

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dream would be similar to the way the NABCG brings together cancer collaborative groups in North America, although in Europe this would have to be without the support of an institution comparable to the NCI.

While initially expected to address a critical need in Europe, the idea of BIG quickly attracted academic breast cancer collaborative groups working in other parts of the world: the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) has been involved from BIG's very first days; the Japanese Breast Cancer Research Group (JBCRG) joined as early as 2004; groups from Latin America in 2006; and in recent years, BIG has attracted the attention of groups based in India, Pakistan and other parts of Asia. Today, one of BIG's strengths is its ability to unite under its umbrella the opinion leaders from 30 countries who share a common vision about the optimal conduct of breast cancer research.

With breast cancer being the most prevalent cancer in women worldwide, global collaboration and a shared vision are necessary to fight this devastating disease efficiently. In this respect, all BIG member groups adhere to the same principles for research conduct. In addition to following Good Clinical Practice guidelines, these include strict rules about scientific integrity in trial design, trial governance, data management, independent data review and the reporting of results. This ensures that BIG research serves to advance knowledge about breast cancer in order to improve treatments and outcomes for patients, preserving at the same time the network's independence from the pharmaceutical and biotechnology industry, even when BIG trials are supported wholly or in part by industry. Balanced partnerships between academic networks, such as BIG, and industry are vital to best serving the needs of patients [1].

BIG's contribution to advancing international breast cancer research

More than 30 clinical trials are currently running or are under development under the BIG umbrella, involving more than 60,000 patients worldwide.

Until recently, BIG has focused mainly on large adjuvant trials looking at questions related to optimal chemo-, hormono- and biological therapies, or to special groups of patients, such as the young or the elderly. This choice has been based on the observation that it is very difficult for a single research group to run clinical trials with enough statistical power, in particular for very specific types of cancer. Examples include studies coordinated by BIG member groups based in Canada (National Cancer Institute of Canada [NCIC] Clinical Trials Group), the UK (Institute of Cancer Research – Clinical Trials & Statistics Unit; National Cancer Research Institute Breast Clinical

Studies Group; International Collaborative Cancer Group) and Switzerland (International Breast Cancer Study Group [IBCSG]) that established the place for aromatase inhibitors in the treatment of early breast cancer [1–3], investigated the role of bisphosphonates in the prevention of metastases [4], or are analyzing the best therapeutic options for premenopausal patients [5], to name but a few.

Beyond the large adjuvant studies, BIG also provides a discussion forum for prevention trials (e.g., IBIS II) and has served as an incubator for trailblazing research in the areas of male breast cancer (in a study being launched with the EORTC) and breast cancer during pregnancy (in a registry run by the German Breast Group). Most recently, BIG has launched a biomarkers and drug development program centered around Phase II studies in the neoadjuvant setting – NeoBIG. These activities will be strengthened in the future to answer the call for faster implementation of knowledge arising from biomolecular and imaging research into clinical practice.

A very important aspect of all BIG trials is that they incorporate a substantial translational research component and emphasize the collection and banking of biological specimens for future research. Without the 'pressure' by a network, such as BIG, to keep trial designs academically sound, the research system would be endangered by the bias towards overly pragmatic studies and/or those driven by economic and regulatory considerations alone.

Among the many studies conducted under the BIG umbrella, several may be considered landmark trials, introducing particularly innovative designs, contributing to significant breakthroughs, or paving the way towards more personalized treatment of the disease. A few are highlighted in the sections that follow.

HERA: a new standard of treatment

BIG 1–01/BO 16348 HERceptin Adjuvant (HERA) Phase III trial is a randomized, three-arm, multicenter comparison of 1 and 2 years treatment with trastuzumab (Herceptin®) versus no trastuzumab in women with *HER2*-positive primary breast cancer who have completed (neo)adjuvant chemotherapy.

HERA demonstrated how major international collaboration can lead to rapid patient accrual and the reporting of results in a record period of time – enrollment to the trial began in late December 2001, and within 4.5 years nearly 5100 women with *HER2*-positive breast cancer were enrolled from 480 sites in 39 countries worldwide. HERA allowed the use of a wide range of approved chemotherapy regimens, and both patients with lymph node-positive and -negative disease were eligible to participate.

The first results of this trial (1 year treatment with trastuzumab after adjuvant chemotherapy) significantly improved disease-free survival among women with *HER2*-positive breast cancer [6], and overall survival [7], together with similar results reported for studies run in the USA [8], led to trastuzumab being registered for use in Europe for women with early breast cancer already within 5 years from the time the first patient entered onto the study. As soon as the results were available, patients on the control arm of the HERA study were offered the possibility to crossover to receive trastuzumab. A total of 52% of patients chose this option.

At present, 1 year of adjuvant trastuzumab is the standard treatment for *HER2*-positive breast cancer patients.

The outcomes of an analysis providing an update of the study continue to show that trastuzumab treatment reduces the risk of breast cancer recurrence in *HER2*-positive patients [9] and confirms its long-term cardiac safety [10]. The final study results reporting the outcome of the 1- versus 2-year comparison are eagerly awaited.

HERA has also been significant by providing an example of a successful partnership between academia and industry in a registration trial. In addition, tumor samples from this trial were collected within the framework of the TransHERA, under which several research projects are now ongoing.

BIG 1–98: answers to important questions for hormone receptor-positive breast cancer

BIG 1–98/IBCSG 18–98 is a multinational, Phase III, double-blind, randomized trial administering adjuvant therapy following complete surgical removal of the tumor to postmenopausal women with hormone receptor-positive breast cancer. Started in March 1998, this study enrolled 8010 women over a period of 5 years.

BIG 1–98/IBCSG 18–98, led and managed under BIG by IBCSG, is the first clinical trial to incorporate both a head-to-head comparison of letrozole with tamoxifen during the first 5 years following breast cancer surgery and the sequencing of both agents, to determine the most effective approach to minimize the risk of recurrence and of side effects.

In 2005, when the trial was first reported, the comparison of letrozole to tamoxifen demonstrated that letrozole was superior to tamoxifen for disease-free survival and time to distant recurrence. After these results were known, approximately 25% of the patients on the tamoxifen arm selected the option of crossing over to letrozole.

The updated results of this trial show a continuing advantage in terms of disease-free survival for patients on letrozole, as well as a strong trend for improved survival [11,12]. Central collection of tumor blocks for over 80% of the patients in BIG 1–98 supports a major program

of translational research studies, the first of which demonstrated that a CYP2D6 phenotype of reduced metabolism was not associated with breast cancer recurrence among tamoxifen-treated postmenopausal women [13].

Another strength of this trial, which has so far produced the best evidence on letrozole and tamoxifen and their safety profiles, is its strong methodology and design that allowed for the collection of substantial baseline and long-term toxicity data.

MINDACT: testing new technology to reduce overtreatment with adjuvant chemotherapy

BIG 3–04/EORTC 10041 Microarray In Node-Negative and 1–3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) is a prospective, randomized study comparing a 70-gene microarray signature (Mammaprint®) to the common clinical-pathological criteria used in selecting patients for adjuvant chemotherapy [14].

This innovative, international study was launched by TRANSBIG (a European Commission supported research consortium founded by BIG) and is sponsored and coordinated by the EORTC. It is BIG's first major 'omics' trial, using microarray technology to better determine which women really need adjuvant chemotherapy. Specifically, it will evaluate this technology by comparing the signature-based test with the traditional method of deciding whether chemotherapy should be prescribed after surgery.

An evaluation of MINDACT took place in November 2008 once the first 800 patients had been enrolled. The results of this 'pilot' demonstrate that the trial, despite its logistical complexity, is both well received by patients and physicians and is collecting high quality data and biological materials for translational research [15]. Enabling researchers worldwide to access genomic data and specimens for future research projects, MINDACT represents a role model for biomaterial collection. In total, 6000 patients will be recruited throughout Europe, and the first results of the entire trial are expected from late 2015.

ALTTO/NeoALTTO: the integration of translational research & strength of international collaboration

BIG 1–06/EGF106903 Neoadjuvant Lapatinib and/or Trastuzumab Treatment Organisation (NeoALTTO), coordinated by the BrEAST Data Center and the BIG member group Grupo Español de Estudio, Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos (SOLTI), is a randomized, multicenter, open-label Phase III study of neoadjuvant lapatinib, trastuzumab and their combination plus paclitaxel in women with *HER2*-positive primary breast cancer.

Randomizing its first patient in January 2008, NeoALTTO rapidly reached its recruitment target of 450 patients (December 2009), and presented its first results at the San Antonio Breast Cancer Symposium in 2010 [16]. In NeoALTTO, significantly higher pathological complete response (pCR) rates were found when patients were treated with two anti-*HER2* agents – lapatinib and trastuzumab – and chemotherapy rather than just one (trastuzumab with chemotherapy or lapatinib with chemotherapy).

Beyond having reached its primary objective, the real strength of the trial lies in its tremendous translational research potential, with fresh and paraffin-embedded tumor samples, as well as frozen serum and plasma having been collected from all patients at baseline, week 2 and at surgery, allowing us to look for biomarkers or gene changes predicting sensitivity/resistance to anti-*HER2* drugs. Research focused on gene expression profiling, circulating tumor cells and FPG-PET/CT imaging is being undertaken, and results from this work are eagerly awaited.

NeoALTTO's companion study is BIG 2–06/ N063D/EGF 106708 Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO), a global randomized Phase III trial involving 1239 sites from 43 countries worldwide that will enroll over 8000 patients and compare lapatinib, trastuzumab, their sequence and/or their combination in patients with early *HER2*-positive breast cancer; the study aims to answer many of the questions left unanswered by research with trastuzumab to date.

Crucial to this study is the planning for translational research upfront in its protocol: paraffin-embedded tumor and blood samples will be obtained from all 8000 patients. Similar to NeoALTTO, the biological materials collection in ALTTO represents a tremendous resource for future translational research, including analyses of circulating tumor cells and work in proteomics in a small subset of patients.

Since the first randomized patient in June 2007, ALTTO's overall accrual has far exceeded all expectations. As of early 2011 recruitment is still ongoing in North America, but screening is expected to close by May 2011. ALTTO is the first large-scale collaboration between the BIG network and the US NCI and the NABCG, reinforcing the strength of broader international cooperation in the conduct of clinical trials.

IMPAKT Breast Cancer Conference

In 2009 BIG, jointly with the European Society of Medical Oncology (ESMO), launched the IMPAKT Breast Cancer Conference, focusing on translational research in breast cancer and on innovative ways of developing new agents. To keep pace with advances in

translational research and its impact on clinical care of breast cancer patients, today it is imperative for basic researchers to understand and address clinical challenges and for physicians to possess the knowledge and skills to integrate and use new technologies. In this regard IMPAKT is a valuable meeting, because it brings together the leading preclinical and clinical researchers from within and beyond BIG to share their knowledge, resources and findings on the most recent developments. Its relatively small size (~800 participants) allows for highly interactive sessions and time for networking to foster collaborative projects. It also offers a preconference training program for early-career research professionals on topics such as biomarker development, targeted therapies, immunotherapy, new technologies and circulating markers. Building on the success of the first two meetings, the 3rd IMPAKT Breast Cancer Conference will take place 5–7 May 2011 in Brussels (www.impact.org).

Moving towards the future

In line with BIG's strategic plan, BIG is in the process of developing, with several different industry partners, trials with new, targeted biological compounds such as PARP inhibitors and pertuzumab. Initiatives related to NeoBIG include the development of a data-sharing platform and a NeoBIG pilot study. Data sharing will begin to take shape in the context of Driving Excellence in Integrative Cancer Research Through Innovative Biomedical Infrastructures (INTEGRATE), in which BIG is a major partner. Launched in early 2011, INTEGRATE is supported by the European Commission (under FP7) and coordinated by Philips Research. The NeoBIG pilot aims to optimize molecular technologies in the neoadjuvant setting. Supported by a grant from the Breast Cancer Research Foundation this investigation will explore the feasibility of:

- Collecting serial samples from multiple clinical centers and under different shipment conditions
- Testing technologies (standard and innovative) on limited amounts of tumor material

In parallel, BIG is restructuring its approach to running trials: to better reflect and support the enormous growth of the network in recent years, it is distributing the responsibility for individual trials and related projects onto more shoulders, and recently implemented a new governance structure. Finally, a key element of BIG's strategy in the coming years is to provide systematic leadership development opportunities for early career scientists and clinicians, involving them in all BIG activities. This will help shape the future generation of leaders in European and international breast cancer research.

Financial & competing interests disclosure

Cecilia Waldvogel and Carolyn Straehle are employees of Breast International Group (BIG). The authors have no other relevant affiliations or financial involvement with any organization or entity with

a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary**BIG's creation: vision & challenges**

- The Breast International Group (BIG) was founded as a nonprofit network of collaborative groups in the 1990s to address fragmentation in European breast cancer research, and today gathers like-minded research groups from around the world. Adhering to the same principles of research conduct, BIG members strive to achieve balanced partnerships between academia and industry in order to best serve the needs of patients.

BIG's contribution to advancing international breast cancer research

- There are more than 30 clinical trials running or in development under the BIG umbrella, involving more than 60,000 patients worldwide.
- Although a leader in large adjuvant trials of chemo-, hormone- and biological therapy, BIG is also a trailblazer for research in other areas.
- BIG trials, of which several are considered landmarks, incorporate a substantial translational research component and emphasize the collection and banking of biological specimens for future research.

HERA: a new standard of treatment

- In less than 5 years, this trial randomized nearly 5100 patients with early *HER2*-positive breast cancer from 480 sites in 39 countries to treatment with trastuzumab (1 or 2 years) versus no trastuzumab.
- First results showed significantly improved disease-free survival and overall survival for patients treated with trastuzumab and contributed to the drug being registered for use in Europe for women with early *HER2*-positive breast cancer within 5 years of study start.
- HERA is an important example of a successful partnership between academic and industry in a registration trial.

BIG 1-98: answers to important questions for hormone receptor-positive breast cancer

- Run under BIG by the IBCSG, this trial comparing letrozole to tamoxifen recruited 8010 patients in 5 years and showed that letrozole was superior to tamoxifen for disease-free survival and time to distant recurrence.
- With collection of tumor blocks for over 80% of patients, this study supports a major program of translational research studies.
- The trial's strong methodology and design has allowed for the collection of substantial baseline and long-term toxicity data, and provides the best evidence on the two drugs and their safety profiles to date.

MINDACT: testing new technology to reduce overtreatment with adjuvant therapy

- Launched by BIG under its European Commission-supported consortium TRANSBIG and sponsored/coordinated by the EORTC, this trial with a target of 6000 patients will use microarray technology to better determine which women really need adjuvant chemotherapy.
- Results of MINDACT's pilot phase show that despite its logistical complexity, the trial is collecting high quality data and biological materials for translational research.

ALTO/NeoALTO: the integration of translational research & strength of international collaboration

- Both of these trials investigate the use of dual anti-*HER2* inhibition with lapatinib and trastuzumab in early breast cancer.
- The 450-patient neoadjuvant study NeoALTO has already shown that significantly higher pathological complete response was found when patients with *HER2*-positive disease were treated with the two agents, but its real strength lies in its tremendous translational research potential.
- ALTO, enrolling over 8000 patients in the adjuvant setting, aims to answer many of the questions hitherto unanswered by research with trastuzumab.

IMPAKT breast cancer conference

- IMPAKT is the conference organized by BIG and European Society of Medical Oncology (ESMO) focusing on translational research in breast cancer and on innovative ways to develop new anticancer agents.
- It gathers leading preclinical and clinical researchers, allows for highly interactive sessions, and offers a preconference training program in translational research for early-career researchers.

Moving towards the future

- BIG has launched a program of innovative trials in the neoadjuvant setting (NeoBIG), including initiatives related to data sharing and a pilot study aimed at optimizing molecular technologies.
- BIG has been restructuring to better reflect and support the enormous growth of the network in recent years, including systematic leadership development opportunities for early-career scientists and clinicians.

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